The role of immunosuppression in squamous cell carcinomas arising in seborrheic keratosis

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Background: Seborrheic keratoses (SK) are common skin neoplasms considered to be benign. Reports of associated squamous cell carcinoma arising within seborrheic keratosis (SCC-SK) have been described.

Objective: To describe the histopathologic characteristics of SCC-SK and identify predisposing factors in formation of these rare lesions.

Methods: There were 162 cases of SCC-SK in a span of a decade (2003-2014). All of the histopathologic specimens and medical records were reviewed. Data from these patients were compared to a control group with seborrheic keratosis who were matched by age, sex, and location of lesion from the same time period (n = 162).

Results: SCC-SK has the classic histopathologic features of SK, such as hyperkeratosis, parakeratosis, papillomatosis, and pseudohorn cysts. The areas of squamous cell carcinoma were characterized by areas of squamous dysplasia (100%), hypogranulosis (79.6%), squamous eddies (79.6%), solar elastosis (80.9%), and brown pigmentation (59.9%).
Patients with a history of immunosuppression had an increased risk for developing SCC-SK (19% vs 3%; $P < .01$), particularly when inhibition was transplant-associated (10% vs 0%; $P < .01$).

Limitations: This was a single center, retrospective study.

Conclusion: SCC-SK occurs more often in elderly men with a history of immunosuppression associated with organ transplants. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.12.002.)

Key words: elderly men; immunosuppression; malignant transformation; SCC-SK; seborrheic keratosis; squamous cell carcinomas; transplant.

Seborrheic keratoses (SK) are common benign skin neoplasms that develop from the accumulation of normal keratinocytes between the basal layer and keratinizing surface. They typically present as stuck on verrucous plaques with variable thickness and pigmentation. SKs were once considered senile warts, but their incidence among younger

Abbreviations used:

CI:	confidence interval
OR:	odds ratio
SCC-SK:	squamous cell carcinoma arising in seborrheic keratosis
SK:	seborrheic keratosis

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patients is rising.[1] The etiology of SK remains unclear, with associations made to human papillomavirus, melanocyte hyperplasia, genetic predisposition, and sun damage.[1]

Patients are typically reassured that these lesions are considered benign; however, they mighy not all be benevolent. The first report of malignant transformation of SK into squamous cell carcinoma was by Civatte in 1954, and since then, many case reports and small studies have been reported on the subject.[1-7] Initially, a question was raised whether these were simply collision tumors due to the relative frequency of both lesions, or if these squamous cell carcinomas actually arise in the seborrheic keratosis.[5] To shed light on this issue, we studied the histopathologic characteristics of squamous cell carcinomas arising in seborrheic keratosis (SCC-SK) and analyzed the demographic characteristics of affected patients.

CAPSULE SUMMARY

- Squamous cell carcinomas can arise in seborrheic keratoses.
- Squamous cell carcinoma arising in seborrheic keratosis (SCC-SK) arises on the head and neck of elderly men with a history of immunosuppression.
- Clinicians should be aware of the possibility of malignancy arising in seborrheic keratoses of transplant patients.

METHODS AND MATERIALS

This study was approved by the Cleveland Clinic Institutional Board Review. All patients with a histologic diagnosis of SCC-SK in the period from 2003 to 2014 were identified through a computer-generated search by using the phrase "seborrheic keratosis and SCC" in pathologic findings from the Cleveland Clinic database (n = 162). Epidemiologic data were collected on age, sex, location of lesion, smoking, history of warts, history of immunosuppression, and history of skin cancer and other cancers. The epidemiologic findings in the SCC-SK group were compared with a control group of patients with diagnosis of seborrheic keratosis matched by age (within 1 year), sex, and location identified from a computer search by using the phrase "seborrheic keratosis" (n = 162).

Histologic review of slides was done independently by 3 dermatopathologists (NAM, KN, WFB). The histologic data collected were examined for the presence of hyperkeratosis, parakeratosis, papillomatosis, hypergranulosis or hypogranulosis, pseudohorn cysts, squamous eddies, cytologic atypia, mitotic figures, solar elastosis, desmoplasia, acantholysis, presence and type of infiltrate, demarcation, pigmentation, and extension of the squamous cell carcinoma invasion. Irritated/inflamed seborrheic keratoses were distinguished from squamous cell carcinoma in situ by the presence of mitotic figures, pleomorphism, and bowenoid dysplasia.

Data are presented as mean ± standard deviation and percentages unless otherwise noted. Comparisons of the clinical variables between patients with SCC-SK and SK were performed by T-test. Categorical variables were calculated by Chi square or Fisher's exact test, as appropriate.

RESULTS

SCC-SK was more commonly found in men (Table I). Most common locations of SCC-SK were on the head and neck, followed by trunk, lower extremity, and upper extremity (Figs 1 and 2). The patients who developed SCC-SK were more likely to have had a prior skin cancer (55.6% vs 43.8%, $P = .03$) and to have gotten a diagnosis of skin cancer at a young age (69.55 vs 7.90, $P < .001$).

Development of SCC-SK was associated with a history of immunosuppression in 19% of cases (odds ratio [OR] 7.43, 95% confidence interval [CI] 2.81-15.5; $P < .001$). Medication-associated immunosuppression was due to prednisone (n = 13) and cyclosporine (n = 1) in the SCC-SK group, while it was due to prednisone (n = 3) and methotrexate (n = 2) in the control group. One person in the SCC-SK group was HIV positive.

Transplant patients, in particular, developed SCC-SK in much higher numbers compared with the control group (10% vs 0%, $P < .001$). The transplants received by patients in the SCC-SK group were solid organs: kidney (n = 7), heart (n = 6), lung (n = 2), and liver (n = 1). The immunosuppressants received posttransplantation were combination prednisone/tacrolimus (n = 7), prednisone/cyclosporine (n = 2), prednisone/mycophenolate (n = 2), sirolimus/prednisone (n = 2), tacrolimus/mycophenolate (n = 1), and cyclosporine/mycophenolate (n = 1). None of these patients had a recorded history of warts or human papilloma virus (HPV) infection.

Histologically, SCC-SKs have a combination of SK and SCC features. The growth pattern was most often a mixture of exophytic and endophytic (40%). The features of SK present in SCC-SK are hyperkeratosis, parakeratosis, papillomatosis, and pseudohorn cysts (Table II; Fig 3).

Associated SCC areas were in situ (49%), invasive (39%), bowenoid (1%), or uncertain because of